Are Broad-Spectrum Fluoroquinolones More Likely To Cause *Clostridium difficile*-Associated Disease?

Irfan A. Dhalla,[1,8]* Muhammad M. Mamdani,[2,7,8]† Andrew E. Simor,[1,3,4,5]
Alex Kopp,[8] Paula A. Rochon,[1,6,7,8] and David N. Juurlink[1,4,7,8]

Department of Medicine,[1] Department of Pharmacy,[2] Department of Laboratory Medicine and Pathobiology,[3] and Department of Health Policy, Management, and Evaluation,[7] University of Toronto, Toronto, Ontario, Canada; Department of Medicine[4] and Department of Microbiology,[5] Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; Kunin-Lunenfeld Applied Research Unit, Baycrest Research Centre for Aging and the Brain, Toronto, Ontario, Canada[6]; and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada[8]

Limited evidence suggests that broad-spectrum fluoroquinolones such as gatifloxacin and moxifloxacin are more likely to cause *Clostridium difficile*-associated disease than levofloxacin. In a population-based case-control study of outpatients prescribed fluoroquinolones, we found no increased risk of *C. difficile*-associated disease requiring hospitalization among patients prescribed gatifloxacin or moxifloxacin compared to levofloxacin.

Clostridium difficile is a gram-positive, spore-forming anaerobe responsible for a wide spectrum of disease ranging from mild diarrhea to fulminant colitis and death (26). Antibiotics are widely recognized as the leading cause of *C. difficile* infection (4). Both the incidence and severity of *C. difficile*-associated disease appear to be increasing (3, 8, 22, 23, 25).

Although fluoroquinolone antibiotics were initially thought to confer only a low risk for *C. difficile*-associated disease (12), recent studies identify them as one of the most commonly implicated antibiotic classes (17, 20, 21, 23, 24). However, fluoroquinolones remain popular because of their broad antimicrobial activity, favorable adverse effect profile, and excellent oral bioavailability. The "respiratory fluoroquinolones" (10), levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin, continue to be recommended as first-line therapy for community-acquired pneumonia (18) and for exacerbations of chronic obstructive pulmonary disease (19).

In part because fluoroquinolones are the most commonly prescribed antimicrobials in the United States (16), differences in the risk of *C. difficile*-associated disease attributable to individual fluoroquinolones would have significant public health implications. Because newer fluoroquinolones such as gatifloxacin and moxifloxacin exhibit better activity versus anaerobic organisms than older fluoroquinolones (2), it has been hypothesized that the newer fluoroquinolones may have different effects on intestinal flora and may be more likely to cause *C. difficile*-associated disease (11). Three studies have produced preliminary data supporting this hypothesis (5, 11, 17).

To further explore this hypothesis, we conducted a population-based nested case-control study using the health care records of approximately 1.6 million older Ontario residents over a 3-year period to determine if community-acquired *C. difficile*-associated disease was more strongly associated with gatifloxacin and moxifloxacin than with levofloxacin.

Setting and design. We conducted a nested case-control study by linking multiple health care databases over 3 years (1 April 2002 to 31 March 2005) in Ontario, Canada. Approximately 1.6 million Ontario residents are aged 65 years or older (28). These individuals have universal access to prescription drug coverage in addition to hospital care and physician services, and their health care utilization patterns can be analyzed anonymously using encrypted health card numbers. This research project was approved by the research ethics board of Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Data sources. We examined data from the Ontario Drug Benefit (ODB) Program, which contains information on prescription drugs dispensed to all Ontario residents aged 65 years or older. The ODB database is extremely accurate, with an overall error rate of less than 1% (15). We used the Canadian Institute for Health Information Discharge Abstract Database to obtain hospitalization data, the Registered Persons Database to obtain demographic data and vital status, and Statistics Canada census data to estimate neighborhood socioeconomic status. These databases have been used previously to study a wide variety of population-based health outcomes (1, 13, 14).

Identification of cases and controls. We restricted our analysis to individuals who received an outpatient prescription for any of the four fluoroquinolones commonly used to treat respiratory infections (levofloxacin, moxifloxacin, gatifloxacin, and ciprofloxacin) during the study period. Among these patients, we defined case patients as those admitted to hospital with a diagnosis of *Clostridium difficile*-associated disease (*International Statistical Classification of Diseases and Related Health Problems*, *10th revision* [ICD-10-CA], code A04.7) within 30 days of the prescription-dispensing date (7). We excluded instances of *C. difficile*-associated disease that arose after hospitalization. The admission date served as the refer-

* Corresponding author. Mailing address: 35 Fernwood Park Ave., Toronto, Ontario M4E 3E9, Canada. Phone: (416) 699-5973. Fax: (416) 480-6048. E-mail: irfan.dhalla@utoronto.ca.
† Present address: Pfizer, Inc., New York, N.Y.

ence date for all analyses. For each case, we randomly selected up to 10 controls who were alive on the index date and who had no hospitalization involving *C. difficile*-associated disease during the preceding 60 days. Controls were matched to cases by age (within 1 year), sex, and receipt of a fluoroquinolone within 30 days prior to the index date.

Exclusions. To avoid incomplete medication records, we excluded individuals during their first year of eligibility for prescription drug benefits (age 65). We also excluded patients hospitalized within 60 days prior to their index hospitalization to avoid the potential confounding effects of regional *C. difficile* outbreaks and because we could not determine medications administered to hospitalized patients. Finally, to restrict our observations to patients treated with a single fluoroquinolone, we excluded patients who received any additional antibiotics in the 60 days preceding the index date.

Statistical analysis. We used conditional logistic regression to estimate the odds ratio for the association between *C. difficile*-associated disease and previous treatment with the various fluoroquinolones, using levofloxacin exposure as the reference category. The two comparison groups were gatifloxacin and moxifloxacin (combined because the number of cases was smaller than expected and because of their similar antimicrobial activity) (17, 29) and ciprofloxacin.

Multivariable analysis was used to adjust for potential confounding variables, including diabetes treated with medication, dialysis, immunosuppressive medications, oral corticosteroid therapy, antineoplastic medications, treatment with a proton pump inhibitor (9), or treatment with an H_2-receptor antagonist within 1 year of the index date. We also adjusted for residence in a nursing home, any hospitalization for malignancy within 2 years of the index date, the socioeconomic status of the patient's neighborhood, and the number of medications dispensed in the previous year as a validated measure of comorbidity (27).

Findings. During the 3-year study period, we identified 96 individuals hospitalized for *C. difficile*-associated disease within a month of outpatient treatment with a fluoroquinolone and 941 matched controls with fluoroquinolone use but no such hospitalization. The characteristics of cases and controls are shown in Table 1. The median age of case patients was 80 years (interquartile range [IQR], 76 to 84 years), and 45% were male. The median length of hospital stay for cases was 12 days (IQR, 6 to 23 days), and 16 cases (17%) admitted with *C. difficile*-associated disease died in the hospital.

We found no significantly increased risk of *C. difficile*-associated disease among patients prescribed gatifloxacin or moxifloxacin as compared to levofloxacin (Table 2). After adjusting for potential confounding variables, the combined odds ratio estimate for gatifloxacin and moxifloxacin compared to levofloxacin was 1.37 (95% confidence interval [CI], 0.75 to 2.49). The adjusted odds ratio for ciprofloxacin as compared to levofloxacin was 1.00 (95% CI, 0.59 to 1.70).

Conclusions. In a large population-based study over 3 years, we found no evidence that outpatient use of gatifloxacin or moxifloxacin was associated with a significantly increased risk of *Clostridium difficile*-associated disease compared to levofloxacin.

Our findings contrast with those of Loo et al. (17), who found that moxifloxacin and gatifloxacin were collectively al-

TABLE 1. Characteristics of cases and controls in this study[a]

Characteristic	Result for[b]:	
	Cases (n = 96)	Controls (n = 941)
Age (yr)		
Mean	80	80
IQR	76–84	75–83
No. (%) male	43 (44.8)	417 (44.3)
No. (%) residing in a nursing home	20 (20.8)	186 (19.8)
No. of medications dispensed in previous yr		
Median	17	13
IQR	13–24	9–19
No. (%) with comorbidities		
Diabetes	17 (17.7)	142 (15.1)
End-stage renal disease	≤5	≤5
Malignancy-related hospitalization	≤5	33 (3.5)
No. (%) with medication type dispensed in previous yr		
Chemotherapy	6 (6.3)	13 (1.4)
Immunosuppressants	≤5	≤5
H_2 receptor antagonists	19 (19.8)	182 (19.3)
Proton pump inhibitors	33 (34.4)	292 (31.0)
Corticosteroids	29 (30.2)	185 (19.7)
Length of stay in hospital (days)		
Median	12	NA
IQR	6–23	
No. (%) of deaths in hospital	16 (16.7)	NA

[a] Exact numbers for cells with fewer than 6 individuals have been suppressed in accordance with Ontario privacy legislation.
[b] NA, not applicable.

most 6 times more likely than levofloxacin to be associated with *C. difficile*-associated disease. However, their observations were derived from a single, predominantly clonal outbreak, whereas we studied *C. difficile*-associated disease over 3 years in a large outpatient population. Also, because most of their case patients received multiple antibiotics, it is possible that some of their patients received gatifloxacin or moxifloxacin as a second-line antibiotic, whereas those who received levofloxacin may have received it as a first-line treatment. Antimicrobial polypharmacy in the Loo study might have confounded the risk estimate for each antibiotic (30). Because of our study design, we were able to limit our analysis to patients who received only one antibiotic. While the size of our study was similar to theirs, 128 (54%) of their case patients and 75 (32%) of their controls had received fluoroquinolones, as compared to all subjects (96 case patients and 941 controls) in our study.

In the only other published study exploring differential effects of fluoroquinolones on the risk of *C. difficile*-associated disease, 10 of 58 patients residing in a nursing home developed *C. difficile*-associated disease during a period when levofloxacin was the principal fluoroquinolone being used (corresponding to an incidence of 17%), compared with 14 of 47 patients during a period when gatifloxacin was the fluoroquinolone of choice (an incidence of 30%) (11). Although this difference

TABLE 2. Fluoroquinolone use and hospitalization for *C. difficile*-associated disease

Antibiotic	No. (%) with antibiotic use within 30 days		Odds ratio (95% CI)	
	Cases (n = 96)	Controls (n = 941)	Unadjusted	Adjusted[a]
Levofloxacin	28 (29)	266 (28)	1.00 (reference)	1.00 (reference)
Ciprofloxacin	44 (46)	286 (52)	0.85 (0.52–1.41)	1.00 (0.59–1.70)
Gatifloxacin or moxifloxacin	24 (25)	189 (20)	1.23 (0.69–2.19)	1.37 (0.75–2.49)
Gatifloxacin	8 (8.3)	57 (6.1)	1.33 (0.58–3.05)	1.46 (0.62–3.44)
Moxifloxacin	16 (16.7)	132 (14.0)	1.18 (0.61–2.27)	1.32 (0.67–2.61)

[a] Multivariate adjustment includes terms for number of medications dispensed in the previous year; diabetes; end-stage renal disease; treatment with immunosuppressive medications, oral corticosteroid therapy, antineoplastic medications, proton-pump inhibitor, and H_2-receptor antagonists; residence in a nursing home; malignancy-related hospitalizations; and neighborhood socioeconomic status.

was statistically significant, the observations were uncontrolled and prone to multiple temporally confounding influences.

There are at least two potential explanations why our findings differ from the reports described above. First, our study included only cases of community-acquired *C. difficile*-associate disease severe enough to warrant hospitalization, whereas the previous studies were predominantly of hospital-acquired *C. difficile*-associated disease. The risk factors for these two entities may be different, and a true association between broad-spectrum fluoroquinolones and the development of *C. difficile*-associated disease may exist in one of these settings but not in the other. Second, our finding of no differential risk of gatifloxacin and moxifloxacin may reflect type II error. However, this seems unlikely given our sample size and also because the odds ratio observed for the combination of gatifloxacin and moxifloxacin was only marginally higher than that seen with levofloxacin. In other words, if there is a true difference in the risk of *C. difficile*-associated disease with individual fluoroquinolones, the confidence interval surrounding our estimated odds ratio implies that this difference is not nearly as large as that suggested by previous research.

Our study has several limitations that merit emphasis. One potential limitation is the restriction to cases of *C. difficile*-associated disease that developed among outpatients and resulted in hospitalization. Although there are other clinically relevant presentations of *C. difficile*-associated disease (e.g., nosocomial infection), the advantage of studying outpatients is that we were able to limit our analyses to patients who had received only one antibiotic and who had not been part of a nosocomial outbreak. Another limitation of our study is that cases were defined using population-based administrative data rather than laboratory detection of *C. difficile* toxins. This limitation might have led us to either underestimate or overestimate the number of cases. Others have also used administrative databases in case-control studies of *C. difficile*-associated disease and have suggested that the reliability of a diagnosis based on administrative data is likely to be excellent (6). Finally, as with all observational studies, our results may be subject to unmeasured confounding. However, we attempted to adjust for many putative risk factors for *C. difficile* to minimize the effect of this limitation.

In summary, we report the first population-based study to test the hypothesis that newer, broad-spectrum fluoroquinolones are more likely to cause *C. difficile* infection among outpatients than levofloxacin. In contrast to previously published studies, we found that gatifloxacin and moxifloxacin were no more likely than levofloxacin to cause *C. difficile*-associated disease. Clinicians will need to continue to balance spectrum of activity, potential side effects, issues of antimicrobial resistance, and cost when deciding which fluoroquinolone to use (31).

REFERENCES

1. **Alter, D. A., C. D. Naylor, P. C. Austin, and J. V. Tu.** 2001. Long-term MI outcomes at hospitals with or without on-site revascularization. JAMA **285:**2101–2108.
2. **Appelbaum, P. C.** 1999. Quinolone activity against anaerobes. Drugs **58**(Suppl. 2):60–64.
3. **Archibald, L. K., S. N. Banerjee, and W. R. Jarvis.** 2004. Secular trends in hospital-acquired Clostridium difficile disease in the United States, 1987–2001. J. Infect. Dis. **189:**1585–1589.
4. **Bignardi, G. E.** 1998. Risk factors for Clostridium difficile infection. J. Hosp. Infect. **40:**1–15.
5. **Biller, P., B. Shank, L. Tkatch, L. Lind, and L. C. McDonald.** 2005. Moxifloxacin use as a risk factor in an outbreak of *Clostridium difficile*-associated disease. Am. J. Infect. Control **33:**E17–E18.
6. **Buchner, A. M., and A. Sonnenberg.** 2002. Epidemiology of Clostridium difficile infection in a large population of hospitalized US military veterans. Dig Dis. Sci. **47:**201–207.
7. **Canadian Institute for Health Information.** 2001. The Canadian enhancement of ICD-10 (International statistical classification of diseases and related health problems, 10th revision). Canadian Institute for Health Information, Ottawa, Canada.
8. **Dallal, R. M., B. G. Harbrecht, A. J. Boujoukas, C. A. Sirio, L. M. Farkas, K. K. Lee, et al.** 2002. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. Ann. Surg. **235:**363–372.
9. **Dial, S., J. A. Delaney, A. N. Barkun, and S. Suissa.** 2005. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA **294:**2989–2995.
10. **Ferrara, A. M.** 2005. New fluoroquinolones in lower respiratory tract infections and emerging patterns of pneumococcal resistance. Infection **33:**106–114.
11. **Gaynes, R., D. Rimland, E. Killum, H. K. Lowery, T. M. Johnson, G. Killgore, et al.** 2004. Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. Clin. Infect. Dis. **38:**640–645.
12. **Gorbach, S. L.** 1999. Antibiotics and Clostridium difficile. N. Engl. J. Med. **341:**1690–1691.
13. **Juurlink, D. N., M. Mamdani, A. Kopp, A. Laupacis, and D. A. Redelmeier.** 2003. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA **289:**1652–1658.
14. **Ko, D. T., M. Mamdani, and D. A. Alter.** 2004. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA **291:**1864–1870.
15. **Levy, A. R., B. J. O'Brien, C. Sellors, P. Grootendorst, and D. Willison.** 2003.

Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can. J. Clin. Pharmacol. **10:**67–71.

16. **Linder, J. A., E. S. Huang, M. A. Steinman, R. Gonzales, and R. S. Stafford.** 2005. Fluoroquinolone prescribing in the United States: 1995 to 2002. Am. J. Med. **118:**259–268.

17. **Loo, V. G., L. Poirier, M. A. Miller, M. Oughton, M. D. Libman, S. Michaud, et al.** 2005. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N. Engl. J. Med. **353:**2442–2449.

18. **Mandell, L. A., J. G. Bartlett, S. F. Dowell, T. M. File, Jr., D. M. Musher, and C. Whitney.** 2003. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin. Infect. Dis. **37:**1405–1433.

19. **Martinez, F. J., and A. Anzueto.** 2005. Appropriate outpatient treatment of acute bacterial exacerbations of chronic bronchitis. Am. J. Med. **118**(Suppl. 7A)**:**39S–44S.

20. **McCusker, M. E., A. D. Harris, E. Perencevich, and M. C. Roghmann.** 2003. Fluoroquinolone use and Clostridium difficile-associated diarrhea. Emerg. Infect. Dis. **9:**730–733.

21. **McDonald, L. C., G. E. Killgore, A. Thompson, R. C. Owens, Jr., S. V. Kazakova, S. P. Sambol, et al.** 2005. An epidemic, toxin gene-variant strain of Clostridium difficile. N. Engl. J. Med. **353:**2433–2441.

22. **McEllistrem, M. C., R. J. Carman, D. N. Gerding, C. W. Genheimer, and L. Zheng.** 2005. A hospital outbreak of Clostridium difficile disease associated with isolates carrying binary toxin genes. Clin. Infect. Dis. **40:**265–272.

23. **Muto, C. A., M. Pokrywka, K. Shutt, A. B. Mendelsohn, K. Nouri, K. Posey, et al.** 2005. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect. Control Hosp. Epidemiol. **26:**273–280.

24. **Pepin, J., N. Saheb, M. A. Coulombe, M. E. Alary, M. P. Corriveau, S. Authier, et al.** 2005. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. Clin. Infect. Dis. **41:**1254–1260.

25. **Pepin, J., L. Valiquette, M. E. Alary, P. Villemure, A. Pelletier, K. Forget, et al.** 2004. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. Can. Med. Assoc. J. **171:**466–472.

26. **Poutanen, S. M., and A. E. Simor.** 2004. Clostridium difficile-associated diarrhea in adults. Can. Med. Assoc. J. **171:**51–58.

27. **Schneeweiss, S., J. D. Seeger, M. Maclure, P. S. Wang, J. Avorn, and R. J. Glynn.** 2001. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am. J. Epidemiol. **154:**854–864.

28. **Statistics Canada.** 20 December 2005, posting date. Population by sex and age group, by province and territory. [Online.] www40.statcan.ca/l01/cst01/demo31a.htm.

29. **Stein, G. E., S. Schooley, K. L. Tyrrell, D. M. Citron, and E. J. C. Goldstein.** 2003. Bactericidal activities of methoxyfluoroquinolones gatifloxacin and moxifloxacin against aerobic and anaerobic respiratory pathogens in serum. Antimicrob. Agents Chemother. **47:**1308–1312.

30. **Wilcox, M. H., and J. Freeman.** 2006. Epidemic Clostridium difficile. N. Engl. J. Med. **354:**1199–1203.

31. **Zhanel, G. G., K. Ennis, L. Vercaigne, A. Walkty, A. S. Gin, J. Embil, et al.** 2002. A critical review of the fluoroquinolones: focus on respiratory infections. Drugs **62:**13–59.